Fungal Meningitis Outbreak

The New England Compounding Center (NECC) in Framingham, Massachusetts has been linked to a national fungal meningitis outbreak in 19 states. Contaminated compounded preservative-free methylprednisolone acetate (80 mg/mL) was produced and distributed by the NECC. Through active surveillance, more fungal meningitis has been identified with another contaminated steroid, epidural injections of triamcinolone acetonide. The fungus *Aspergillus* has been identified; the main fungus, however, is *Exserohilum rostratum*, a rare human pathogen. There have also been reports of *Aspergillus fumigatus* in transplant recipients who received an NECC cardioplegic solution during open heart surgery.

As of October 31, 2012, 29 people have died, 368 people have fallen ill, and nearly 14,000 people are thought to have been exposed. In addition to meningitis, peripheral joint infections have also been reported. Three potentially contaminated lots of methylprednisolone injections were shipped to 75 pain clinics in 23 states, starting May 21. The majority of patients received the injections to treat back pain. The Food and Drug Administration (FDA) is also investigating additional NECC products, including triamcinolone acetonide, ophthalmic injectable drugs, or ones used in conjunction with eye surgery and cardiopulmonary solution products. State and federal inspections in recent weeks have discovered substandard conditions, including unsanitary clean rooms at NECC from mold and bacteria-contaminated surfaces to poor sterilization. NECC has recalled all of its products (over 2,100) and has suspended operations.

Those contaminated steroid products. The CDC recommends collection of cerebrospinal fluid (CSF) for culture and to monitor improvement. More patients with mild disease can use oral therapy, but the intravenous formulation is recommended in more severe cases. The addition of amphotericin B should be considered in patients with severe disease or those unresponsive to voriconazole therapy. A minimum of three months of antifungal therapy should be considered. The CDC is not recommending antifungal treatment in symptomatic patients with normal CSF.

On October 31, Ameridose, an NECC sister company, issued a voluntary recall of any unexpired Ameridose products in circulation. This recall is to cooperate with the FDA and the Massachusetts Board of Registration in Pharmacy in seeking improvements in Ameridose’s sterility testing process.

**Up-Scheduling Hydrocodone-Containing Products**

A public meeting will be held to review the Drug Enforcement Administration’s (DEA’s) finding that hydrocodone-containing products have a similar abuse potential as Schedule II drugs and require regulation. The FDA briefing documents claim that hydrocodone-containing combination products, such as hydrocodone/acetaminophen (e.g., Vicodin®), should be kept as Schedule III controlled substances and not be subject to tighter regulations to prevent abuse. Hydrocodone itself is currently Schedule II. The FDA briefing documents released ahead of this meeting claim that there is insufficient evidence to support this. The FDA’s reasons against up-scheduling hydrocodone include increase in the use of nonsteroidal anti-inflammatory drugs (NSAIDs), increase in Schedule II opioid prescribing, and codeine-containing cough suppressants would be the only option for antitussive opioid combination Schedule III products with the up-schedule. The agency’s Drug Safety and Risk Management Advisory Committee meeting originally scheduled for October 29-30 has been postponed due to extreme weather conditions.

**Accidental Over-The-Counter (OTC) Ingestion**

The FDA has issued a safety warning for pediatric patients who may accidentally ingest OTC ophthalmic drops or nasal decongestants. The warning follows reports of 96 accidental ingestions of products containing tetrahydrozoline, oxymetazoline, or naproxen involving children ages 5 years and younger. With volumes of only 1 to 2 mL, a total of 53 patients required hospitalization for symptoms, including nausea, vomiting, lethargy, tachycardia, decreased respiration, bradycardia, hypotension, hypertension, sedation, somnolence, mydriasis, stupor, hypothermia, drooling, and coma. No deaths have been reported. These products should be stored out of reach of children. In the event of an accidental ingestion, consumers should call the National Capital Poison Center 1-800-222-1222 and seek immediate medical care. A full list of products containing tetrahydrozoline, oxymetazoline, or naproxen is available on the agency’s website.

**FDA Targets Online Pharmacies**

The FDA has targeted online pharmacies, who sell counterfeit and illegal medications, as part of a coordinated international crackdown of this market. According to the Center for Safe Internet Pharmacies, counterfeit drug sales reached $75 billion globally in 2010, a 90 percent increase from 2009. In an international mail screening, the FDA found antibiotics, antidepressants, antianginal agents, and antihypertensives headed to the US. Dronperidone (withdrawn in the US due to severe cardiovascular events), olsentamivir (not generic in the US), isoretinoin, and sildenafil were among the drugs. One-quarter of consumers purchase prescription drugs online. The FDA has launched a consumer website called “BeSafeRx–Know Your Online Pharmacy” in an effort to educate consumers.

**Drug Information Highlights**

- The interleukin-6 (IL-6) inhibitor tocilizumab (Actemra®) has an expanded indication for moderately to severely active rheumatoid arthritis (RA) in adults who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Prior to this new indication, it was indicated in patients with an inadequate response to one or more tumor necrosis factor (TNF) blockers.
- A safety warning has been issued for oxymorphone extended-release (Opana® ER) by the FDA due to reports of thrombotic thrombocytopenic purpura (TTP) with the use of this oral extended-release opioid when it is abused and injected intravenously. Kidney failure requiring dialysis and one death have been reported.
- Guanfacine hydrochloride extended-release (ER), generic for Intuniv®, was approved for the treatment of attention deficit hyperactivity disorder (ADHD) as monotherapy and as adjunctive therapy to other stimulant medications in children 6 years of age and older. Guanfacine ER is dosed orally once daily beginning with the initial titration dose of 1 mg and titrating as needed in increments of 1 mg per day weekly. The maximum dose is 4 mg daily. It is available as 1 mg, 2 mg, 3 mg, and 4 mg tablets.
- Calcipotriene and betamethasone dipropionate topical suspension 0.005%/0.064% (Taclonex®) received an expanded indication for the treatment of plaque psoriasis of the body.
- Calcipotriene (Dovonex®) 0.005% foam received an expanded indication for plaque psoriasis of the scalp.

**Sources:**
- www.ashp.org
- www.medscape.com
- www.cdc.gov
- www.PTCommunity.com
- www.fda.gov
- www.pubmed.gov

**Editorial Staff:**
- Executive Editor: Maryam Tabatabai, PharmD
- Deputy Editors: Donna Johnson, PharmD
- Carole Kerzic, RPh
- Raquel Holmes, RPh

**Contact Information:**
- Maryam Tabatabai, PharmD
- (513) 794-5265 or
- www.MagellanMedicaid.com

**November 2012**
<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Description</th>
<th>Applicant</th>
<th>FDA Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>methylphenidate hydrochloride</td>
<td>Quillivant XR™</td>
<td>The FDA approved Quillivant XR, the first extended-release liquid methylphenidate formulation, for the treatment of attention deficit disorder (ADHD) in children ages 6 to 12 years. The recommended starting dose is 20 mg orally every morning. The dosage may be titrated up in 10 mg to 20 mg increments weekly. The maximum daily dose is 60 mg. Quillivant XR is available as a 25 mg/5 mL oral suspension.</td>
<td>Nextwave</td>
<td>FDA NDA Approval 09/27/2012</td>
</tr>
<tr>
<td>regorafenib</td>
<td>Stivarga®</td>
<td>Regorafenib (Stivarga), an oral tyrosine kinase inhibitor (TKI), was approved for the treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF (vascular endothelial growth factor) therapy, and, if KRAS wild type, an anti-EGFR (antiepidermal growth factor receptor) therapy. Regorafenib has a black box warning for hepatotoxicity that may be severe or even fatal. Monitor hepatic function prior and during treatment. The recommended dose is 160 mg orally daily for the 21 days of each 28-day cycle. Take with a low-fat breakfast. It is available as 40 mg tablets.</td>
<td>Bayer HealthCare</td>
<td>FDA NDA Approval 09/27/2012</td>
</tr>
<tr>
<td>adalimumab</td>
<td>Humira®</td>
<td>The FDA expanded the approved uses for adalimumab to include inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to immunosuppressants, such as corticosteroids, azathioprine, or 6-mercaptopurine (6-MP). The effectiveness of adalimumab has not been established in patients who have lost response to or were intolerant to tumor necrosis factor (TNF) blockers. The initial UC dose is 160 mg, a second dose two weeks later of 80 mg, and a maintenance dose of 40 mg every other week, thereafter. The drug should only be continued in patients who have shown evidence of clinical remission by eight weeks of therapy.</td>
<td>Abbott</td>
<td>FDA sBLA Approval 09/28/2012</td>
</tr>
<tr>
<td>cysteamine</td>
<td>Cystaran™</td>
<td>Cysteamine (Cystaran), a cystine-depleting agent, has been approved for the treatment of corneal cystine crystal accumulation in adult patients with cystinosis. Cystinosis is a genetic disease that causes an abnormally large accumulation of cystine to form as crystals in the patient’s major organs. Oral cysteamine has no effect on ocular cystine accumulation. The recommended dose is one drop in each eye every waking hour. Cysteamine 0.44% ophthalmic solution is available in a 15 mL dropper bottle.</td>
<td>Sigma Tau</td>
<td>FDA NDA Approval 10/02/2012 Orphan Drug Status</td>
</tr>
<tr>
<td>ocriplasmin</td>
<td>Jetrea®</td>
<td>Ocriplasmin (Jetrea), a proteolytic enzyme, is the first pharmacologic and non-surgical treatment indicated for the treatment of symptomatic vitreomacular adhesion (VMA) in adults. Ocriplasmin is an enzyme that breaks down the proteins in the eye responsible for VMA. The recommended dose is 0.125 mg (0.1 mL of the diluted solution) administered by intravitreal injection to the affected eye once as a single dose. It is available in a single-use glass vial containing 0.5 mg ocriplasmin in a 0.2 mL solution for intravitreal injection.</td>
<td>Thrombogenics</td>
<td>FDA BLA Approval 10/17/2012</td>
</tr>
<tr>
<td>oxcarbazepine extended-release</td>
<td>Oxtellar ER™</td>
<td>Oxcarbazepine extended-release (Oxtellar ER) was approved as adjunctive therapy of partial seizures in adults and children ages 6 to 17 years. The recommended daily dose in adults is 1,200 mg to 1,400 mg initiated as 600 mg daily and titrated weekly in 600 mg per day intervals until target dose is achieved. In children, the dose is 8 mg/kg to 10 mg/kg per day. Increase weekly in increments of 8 mg/kg to 10 mg/kg daily, not to exceed 60 mg per day until target dose is reached. Oxcarbazepine ER will be available as 150 mg, 300 mg, and 600 mg ER tablets. Launch is expected in early 2013.</td>
<td>Supernus</td>
<td>FDA NDA Approval 10/19/2012</td>
</tr>
<tr>
<td>perampanel</td>
<td>Fycompa™</td>
<td>The FDA approved perampanel (Fycompa), a non-competitive AMPA glutamate receptor antagonist, as adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older. Perampanel carries a black box warning about the potential risk of serious psychiatric and behavioral adverse reactions. The recommended starting dose is 2 mg once daily at bedtime in patients not on enzyme-inducing antiepileptic drugs (AEDs), such as carbamazepine, oxcarbazepine, and phenytoin, and 4 mg in patients on enzyme-inducing AEDs. The dose may be titrated based on clinical response and tolerability in weekly increments of 2 mg at bedtime. The maximum daily dose is 12 mg. Perampanel tablet strengths are 2 mg, 4mg, 6 mg, 10 mg, and 12 mg.</td>
<td>Eisai</td>
<td>FDA NDA Approval 10/22/2012</td>
</tr>
</tbody>
</table>